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**Adulthood with Turner Syndrome:
Quality of life, psychosocial
adjustment and clinical management in
70 Italian women**

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PREFACE

This work comes from my experience at the Rare Disease Unit in the Pediatric Endocrinological Unit at the Bologna University Hospital where I arrived 10 years ago as a graduate student: my love for clinical psychology, and for the research as well, have grown up there.

First of all, special thanks go to all the patients I have met during these years, they have taught me so much about myself, life and being a psychologist! They are the main characters of this work, those who have made this research possible, the ones to whom I hope this work will be useful in the end. I hope it will be useful to improve our knowledge on Turner syndrome and to develop a better way of taking care of the new generation of girls with Turner syndrome, and in general of the individuals who are somehow 'rare'.

I want to thank professor Laura Mazzanti who has the responsibility of the Rare Disease Unit and the whole staff: Annamaria Perri, Emanuela Scarano and Federica Tamburrino (four extraordinarily competent doctors), Antonella Tedesco, Chiara Mazzari and Monica Guidetti (three wonderful nurses). Their sensitivity and devotion to little patients and their families and their professionalism has made it possible for a psychologist to become part of the daily job of the unit and conceive the research project that I'm going to present in this thesis. They also helped me in the process of developing this research being always the competent, interested and challenging interlocutors any researcher needs.

I also want to thank my tutor, professor Nicolino Rossi, who has encouraged me in my objective of matched clinical leaning and my interest in research as well as my fellow phd colleagues for sharing these three years of work with me. A special thanks is also due to my psychologist colleagues at the Clinical Psychology Unit of the University Hospital of Bologna: Catia, Delia, Federica, Graziana, Laura, Maria Teresa, Nicoletta, Sofia and to the chief of the unit, Doctor Franco D'Alborton for supporting me during the realization of this project.

Last but not least, I'd love to thank my husband Lorenzo and our beloved children, for enduring all the time I spent working on this paper and project during weekends and nights.

INTRODUCTION

This work is composed of three main chapters: the first draws a picture of the literature and the research on psychological aspects of Turner syndrome and tries to describe the rationale of the research presented in chapter 2; the third chapter tries to present some conclusive thought on the issue of research on psychological aspects of Turner syndrome (TS). The present introductory section is dedicated to a brief description of the main characteristics of Turner syndrome's health aspects.

Turner syndrome (TS) is a chromosomal abnormality (total or partial absence of one of the sexual chromosomes in some or all cells of the body), which affects approximately 1:2000 female live births. The principal characteristics are short stature and gonadal dysgenesis resulting in lack of sex hormones, incomplete pubertal development and infertility.

Diagnosis of TS is usually reached with standard banded karyotype, counting 15–30 cells. If low-level mosaicism is suspected, increasing the number of cell count to 100 cells may be necessary, which allows for detection of 3% mosaicism at 95% confidence levels. Only 50% of TS individuals have a 45, X karyotype and 40% will have a structural abnormality of the second X chromosome. Approximately 30% of TS will have a mosaic peripheral blood karyotype, where a 45, X cell line coexists with one non-45, X cell line. Importantly, 10% of women with TS have mosaicisms for a cell line with a normal or abnormal Y chromosome. The risk of gonadoblastoma in these individuals is estimated to be 30% and early gonadectomy is recommended. The majority of women with a TS mosaic karyotype will not have the classical features of TS, and a low threshold for investigations is encouraged to avoid late diagnosis. In many genetic laboratories, DNA microarrays are increasingly used to diagnose TS.

Paediatric clinical management of this condition usually consists of Growth Hormone (GH) treatment from early childhood, in order to enhance final height, and oestrogen replacement therapy (HRT), starting in pre-adolescence, in order to induce development of secondary characteristics and to avoid the symptoms, signs and

sequelae of oestrogen deficiency. Approximately 30% of girls with TS enter puberty spontaneously, but only 4% reach menarche and only 1% are fertile. Almost 90% will require hormone replacement therapy either to initiate and/or to ensure progress in puberty, maintain secondary sexual development and promote bone health. The optimal regimen for sex steroid replacement for induction of puberty in TS remains a controversial issue as well as the timing of introduction of oestrogen, the type, dose and route (oral versus transdermal) of oestrogen administration. The main goals of sex steroid replacement in puberty are to ensure (i) adequate breast development, (ii) pubertal growth spurt, (iii) adequate uterine development and (iv) bone accrual for adequate peak bone mass. Decisions of ongoing oestrogen replacement need to be carefully discussed with the young person and family during transition and management may need to be individualized.

Spontaneous pregnancies are very rare (2%) in women with TS. Advances in reproductive medicine as in vitro fertilization and oocytes cryopreservation are offered to women with TS bringing up new medical, ethical and psychological challenges. With the advent of modern techniques of assisted reproduction technologies, many TS women are seeking the opportunity for childbearing. However, associated medical problems such as AD and autoimmune conditions (e.g. undiagnosed hypothyroidism) may contribute to significant risks in these pregnancies. The likelihood of functional ovarian tissue and fertility in women with TS relies on the presence of 46,XX germ cells in the ovaries and is therefore more likely in women with mosaicism. Women with mosaic TS may also benefit from cryopreservation of patient's own oocytes for fertility preservation before decline in ovarian function.

While short stature, hypogonadism and typical dysmorphic features are commonly recognized clinical features, a range of medical problems have recently come to the attention of clinicians. The focus of recent research is addressing adulthood (Lucaccioni et al., 2014). In Turner syndrome, several medical conditions can exist across the age span: aortic dilatation (AD) and dissection, bone health, hearing loss, liver dysfunction, autoimmune conditions and cancer risks. All these medical issues may have a major impact on the life of these girls and women.

Congenital heart disease (CHD) is a common association of TS and reported in up to 50%. Hypertension is also relatively common and may require careful evaluation with 24 hour blood pressure monitoring. AoD in TS, six times more common than in healthy individuals, occurs frequently in the third decade as opposed to the seventh decade, although paediatric cases are seen. Autoimmune and inflammatory conditions are more common in TS. Hypothyroidism occurs in up to 30%, whereas thyrotoxicosis occurs in <1.6%. Diabetes mellitus is also more common, which may be associated with obesity and metabolic syndrome.

Abnormal liver function with raised ALT and GGT is thought to be related to hepatic steatosis and small intrahepatic vascular anomalies. Otitis media, middle ear effusions often requiring grommets insertion and subsequent cholesteatoma are recognized complications of young girls with TS. Less well recognized is the progressive hearing loss, usually in the high frequency region, especially after the age of 30 years. The rate of decline in TS women aged 30–60 years is equivalent to that of 70–80 years in non-TS women.

In addition, women with TS appear to be at increased risk of cancers especially CNS tumours, bladder and urethral cancers.

Consequently to the health implications described above, women with TS are involved in complex programmes of follow-up from childhood.

Finally, regarding the life expectation of women with TS, a recent study (Stochholm et al. 2012), states that the increased mortality they found in TS was not materially affected after adjustment for cohabitation and education.

CHAPTER 1

BACKGROUND: A REVIEW OF THE LITERATURE ON PSYCHOLOGICAL ASPECTS OF TURNER SYNDROME

This chapter contains an accurate review of the studies on psychological aspects in TS. I used the PRISMA statement (Liberati et al., 2009) in order to identify the areas that have been studied and the most important findings.

Studies included were identified by a systematic review of English articles using MEDLINE. No time limit was used. Additional studies were identified, scanning reference lists of articles. The last search was run on 27 January 2015. Only studies which have investigated psychological aspects or psychological intervention in TS were included. Only English papers were included. Search terms included: Turner syndrome matched with psychological, psychosocial, psychotherapy, psychotherapeutic, adjustment, quality of life, well-being, social, adulthood, cognitive, neurocognitive, self-esteem.

I decided to collect and present the studies reviewed in four different groups according to their focus. Finally some methodological considerations are drawn.

1 TURNER SYNDROME AS A PERFECT MODEL FOR INTERACTION OF COGNITION, HORMONES, BRAIN AND GENES

Burnet, Reutens, and Wood (2009) note that the research on the neural basis of cognition is considering TS as an important model with which to explore the interaction between genes, hormones, brain development and human behaviour. Due to its genetic characteristics (in TS the normal process of X-inactivation is bypassed, resulting in the exclusive expression of genes produced by a single X-chromosome, which is either paternally or maternally inherited), TS has been used to investigate the impact of genomic imprinting (the process by which some genes are

preferentially activated depending on their paternal or maternal origins) on cognition. So far, the results in this field are inconsistent: Skuse et al. (1997) reported evidence that social cognitive deficits in Turner syndrome are the result of an imprinted X-linked locus. TS patients with a paternally driven X chromosome had superior verbal and higher executive skills that mediate social interaction. On the contrary, in an earlier study by Lepage, Hong, Hallmayer, and Reiss (2012b) on 65 children with TS, there were no effects of genomic imprinting on standardized measures of social cognition; and in a study by Sheaffer, Lange, & Bondy (2008), sexual functioning was not correlated with maternal or paternal X origin.

The neurocognitive profile of TS during childhood has been widely researched in the past two decades. TS is not typically associated with mental retardation. The research is consistent in describing the TS population as having an average to low-average full-scale IQ. Most of the studies used the Wechsler Intelligence Scales. Besides this normal IQ, there seems to be a specific neuropsychological profile associated with TS, although its precise etiology and nature are not yet fully understood (Swillen et al., 1993; Boman, Moller, & Albertsson, 1998; Hong, Kent, & Kesler, 2009; Lepage, Dunkin, Hong, & Reiss, 2011). Despite verbal abilities being normal, impaired executive function and selective deficits in visual-spatial reasoning skills, in motor function, in nonverbal memory and in attention have been reported in several studies (Ross, Zinn, & McCauley, 2000b). Difficulties in these domains could have a significant impact on long-term academic and adaptive functioning in affected individuals. As an example, girls with TS lag behind peers in math achievement (Rovet, Szekely, & Hockenberry, 1994), and are more likely to be diagnosed with attention-deficit disorder and nonverbal learning disorders (Mazzocco, 2006; Russell et al., 2006).

Recent advances in magnetic resonance imaging (MRI) research techniques have begun to elucidate brain differences that may explain this neurocognitive phenotype. This includes a range of findings including volumetric differences in cortical gray matter, aberrant structure of white matter tracts connecting these cortical regions, and differences in brain activation patterns during cognitive tasks related to visuospatial, executive and social cognitive functions.

Some research has tried to examine the amygdala in TS but, as with genomic imprinting, the results so far have not led to a clear conclusion. Burnett et al. (2010), reviewing the research on this issue, argue that the lack of clear imprinting effects on amygdala integrity in TS women suggests that alternative mechanisms may contribute to the reported perturbations. Lawrence et al. (2003a) suggest that, since the amygdala is a structure with abundant oestrogen receptors, the effect of oestrogens in early life should be investigated.

More recently research has focused attention on social cognition and adaptive living skills in TS. They seem similarly impacted. Parents of young girls with TS report that their daughters have significantly more difficulty in social interactions compared to peers (Hong, Dunkin, & Reiss, 2011). The research studies into cognitive functioning in adult women with TS are less numerous, even if it seems that this specific profile persists in adulthood (Downey, Ehrhardt, Gruen, Bell, & Morishima, 1989; McCauley, Sybert, & Ehrhardt., 1986; Delooz, Van der Berghe, Swillen., Kleczkowska, & Fryns, 1993; Ross et al., 2002; Lagrou et al, 2006).

A certain number of studies has described atypical social cognition in TS: deficit in facial recognition has often been noted (Lawrence, Kuntsi, Coleman, Campbell, & Skuse, 2003b; Ross, Kutshner, & Zinn, 1997; McCauley, Kay, Ito, & Treder, 1987; Mazzocco, Baumgardner, Freund, & Reiss, 1998; Lawrence et al., 2003b), particularly with respect to the expression of fear and anger (Mazzola et al., 2006; McCauley et al., 1987; Hong, Signe Bray, Haas, Hoeft, & Reiss, 2014). In contrast in a recent study on 42 young girls with TS, Hong et. Al. (2011) didn't detect affect recognition abnormalities, even when the TS girls were compared to age-matched controls. This study, however, demonstrated that TS individuals have significantly decreased social competency on all dimensions of the Social Responsiveness Scale, and on the Social Perception domain of the NEPSY. Other components of face processing (eye-tracking and gaze fixation) have been reported to be impaired in TS subjects compared to controls (Lawrence et al., 2003b; Mazzola et al., 2006). Hong et al. (2011) also found lowered memory for faces in TS children.

In my opinion, considering the small and heterogeneous samples used in this field of

research we are not able to draw specific conclusions. I can say that this data seems to point to the hypothesis of a TS social cognitive profile, which could underlie the psychosocial problems found in the TS population (McCauley et al., 1987).

Both the fundamental genetic influence of X-monosomy and the still completely unknown role of hormones on brain development are complex and likely to interact with other genetic liabilities, epigenetic and environmental factors and warrant ongoing examination in future research.

2 A SECOND PERSPECTIVE OF THE RESEARCH: LIVING WITH TURNER SYNDROME

The point of view of women with TS as well as the challenges of parents in raising these girls and emotional difficulties that women with TS have to face received relatively little attention compared to the research focused on cognitive profile or other psychological constructs. In this paragraph, I will present the studies that investigated psychological constructs and indicators of psychosocial adjustment, then I will review the studies that used a qualitative approach to describe the point of view of women with TS.

Psychosocial adjustment in adults with Turner syndrome

Several studies have investigated psychosocial adjustment of adult women with TS and almost all of them have generically described this population as reasonably satisfied with their employment and social life, emotionally stable, but with some areas of lowered competence (self-esteem, partner relationships and sexual functioning).

Most of the studies in this field consisted of quantitative research based on questionnaires sent by mail with self-rated, standardized instruments. Few studies used direct measurement of social skills or social cognition. Finally, some research compared patients' self-rated competence with their parents rating.

I will briefly review the literature on this issue presenting the findings according to these different measures of psychosocial adjustment and to different methodological paths.

General indicators of psychosocial adjustment

Social adjustment indicators frequently studied in TS women are: level of education and employment; age at time of leaving the parental home; sexual life milestones such as age at first kiss, age at first intercourse and marital status. A divergent socioeconomic profile is apparent, with a reduced proportion of TS individuals finding a partner and becoming mothers. The educational level was similar to controls.

Education and employment

Most studies describe women with TS as at least as educated and employed as the general population (Carel et al., 2005; Naess, Bahr, & Gravholt, 2010, Stockholm et al., 2012) or even more so (Pavlidis, McCauley, & Sybert, 1995; Okada, 1994; Sheaffer, et al. 2008; Verlinde et al., 2004). However, some research showed that TS women had a lower occupational status than would be expected from their level of education (Downey et al., 1989; McCauley, Feuillan, Kushner, & Ross, 2001; Ross et al., 2002). Finally, in a study on 80 TS patients, Naess et al. (2010) found that individuals with TS were more attached to their work compared with age-matched controls.

Sexual life milestones, partner relationships and marital status

All the studies which have researched gender identity reported that girls with TS develop a normal female identity (Pavlidis et al., 1995; Sylvén, Magnusson, Hagenfeld, & Schoultz, 1993; Ehrhardt Greenberg, & Money, 1970) or a more feminine one (Nyborg & Nielsen, 1977; Downey et al., 1989).

Literature is consistent in describing women with TS as having heterosexual orientation (Pavlidis et al., 1995; Sylvén et al., 1993) but as being less likely to be married or have a partner (Aran et al., 1992; Downey et al., 1989; Nyborg & Nielsen, 1977; Okada, 1994; Boman, Bryman, Halling, & Moller 2001; Naess et al., 2010; Pavlidis et al., 1995; Rolstad, Moller, Bryman, & Boman, 2007; Sheaffer et al., 2008; Verlinde et al., 2004, Stochholm et al, 2012). Stochholm et al.'s clinical study on nine hundred and seventy nine TS females shows a strong association between TS, labor market marginalization, economic disadvantage, and singleness in these people. In contrast, Sylvén et al. (1993), in a small sample of middle-aged TS women, found a higher rate of married subjects and argued that women with TS tend to establish partner relationships later in life than the general population. Discordance among studies on marital status might be influenced by cultural differences.

TS women, moreover, report to have their first sexual experience later in life (Naess et al., 2010; Pavlidis et al., 1995; Carel et al., 2006; Rolstad et al., 2007); and several studies showed that these women have a delayed exit from the parental home (Naess et al., 2010; Verlinde et al., 2004; McCauley et al., 1986).

Psychological constructs studied in women with Turner syndrome

Psychological constructs commonly used as outcome indicators in research on adulthood psychosocial functioning in the TS population are: Quality of life (QoL) and Health related Quality of Life (HRQoL), sexual functioning, self-esteem, social anxiety, social skills and social cognition.

QoL and HRQoL

Several studies have addressed Quality of Life in TS women. The large sample of French TS GH treated women (Carel et al., 2005) showed no difference in quality of life compared to reference population data using SF-36 and General Health Questionnaire 12. Also Boman et al. (2001) found that psychological well-being and

self-rated health were similar in 63 Swedish women with TS and in Swedish normative population data, while TS women reported more social isolation than the normative group. Naess et al. (2010) recently reported more health problems in a TS sample than in an age-matched control group, while TS individuals rated a higher degree of satisfaction with their financial and leisure situations, so the authors concluded that TS women seem to cope well with life. Ros et al. (2013) found that TS subjects presented impaired physical QOL compared to healthy subjects.

Recent studies on GH and oestrogen-treated young adult women with TS (Lagrou et al., 2006; Bannik, Raat, Mulder, & De Muinck Keizer-Schrama, 2006) compared to an age-matched group in the first case and to reference data regarding the general female Dutch population in the second case, did not find any difference in behavioural and emotional problems reported by the two groups. Lagrou et al. (2006) underlined that the TS subjects perceived themselves as less socially competent and showed fewer problems in somatic complaints.

Sexual functioning

Individuals with TS result less sexually active than controls or than normative data (Pavlidis et al., 1995); a large number has never had intercourse (45% in Pavlidis et al., 1995), but those with partners have comparable degrees of sexual satisfaction and sexual functioning with respect to gender-based norms (Sheaffer et al., 2008; Downey et al., 1989; Pavlidis et al., 1995). Rolstad et al. (2007) in a sample of 57 TS subjects and Pavlidis et al. (1995) in a sample of 80 TS subjects found that several women with a partner reported sexual problems, but curiously, they unanimously reported being satisfied with their sex life and partner relationship.

Sheaffer et al. (2008) in their study on 98 women with TS, found that two thirds of the sample group did not have a partner. In this group, sexual functioning was extremely low, while sexual fantasy rated average. On the contrary, Rolstad et al. (2007) found that single women with TS differ more from the general population, with respect to sexual desire and sexual activity, than those with a partner.

Sheaffer et al. (2008) found no correlation between sexual functioning and many variables included in the study, such as: spontaneous puberty, hearing loss, age of pubertal induction, use of oestrogens and prevalence of Turner features, karyotype. Height and education, on the other hand, were significant predictors of relatively high sexual functioning in TS subjects non treated with GH. In the study of Ros et al (2013) women with TS resulted less likely to be involved in sexual activity, arousal dysfunctions being their main symptom.

Self-esteem

Self-esteem or self-concept have been widely studied in the TS population. Most of the studies used standardized scales (Piers-Harris self-concept scale; Tennessee self-concept scale; Coopersmith's Self-Esteem Inventory).

The results are consistent in reporting significantly lower self-esteem or self-concept compared to girls of normal stature (McCauley, Ross, Kushner, & Cutler, 1995; Rovet & Holland, 1993; Pavlidis et al., 1995; Van Pareren et al., 2005) and to general population norms (Carel et al., 2006; Pavlidis et al., 1995; Delooz, et al., 1993; McCauley et al., 1986). In their population-based cohort study, Carel et al. (2006) found that self-esteem was negatively associated with otological problems and excess weight, and positively with sexual experience. As regards body satisfaction, in this study there was no association with dysmorphic features.

McCauley et al. (1995) revealed a decline in self-concept for TS girls as they moved from childhood into early adolescence. Ross et al. (1996) found that initiating oestrogen therapy in 16-yr-old adolescents with TS was directly associated with an improvement compared with the baseline self-esteem scores, while this effect was not noticed in an untreated comparison group. Carel et al. (2006) had discordant results: they did not find a positive effect of oestrogens on self-esteem in their cohort study on late adolescent and adult women, they also found that self-esteem and psychological distress are strongly interrelated. Pavlidis et al. (1995) found that self-esteem in adulthood was related to health status.

Social anxiety

Earlier studies on social anxiety in TS based on self reports show that the TS individuals and their parents rated themselves and their daughters as the controls (Mazzocco et al., 1998; McCauley et al., 2001; Ross et al., 1996; Lesniak-Karpiak, Mazzocco, & Ross, 2003; Suzigan, de Paiva e Silva, Guerra-Júnior, Valente Lemos Marini, & Trevas Maciel-Guerra, 2011).

Only one of these studies (Lesniak-Karpiak et al., 2003) assessed social anxiety in a small sample (N=29) of girls with TS compared to a control group, using both rating scales and direct assessment. Social skills were evaluated through the observation of social behaviour in role-plays of representative social situations. Even if self-report and parental ratings did not suggest higher levels of social anxiety in females with TS in this study either, the behavioural indices examined in the role-play showed that the TS individuals made fewer facial movements than the subjects in the comparison group.

Social skills

In their study, Suzigan et al., (2011) compared the social skills of a group of TS women (N=52) to their sisters'. The subjects were given a questionnaire to complete; their mothers' perception of their daughters' social skills was collected by interview. No difference was found between TS females (aged 15-35) and their sisters regarding knowledge about performance in interpersonal situations, and even though their mothers rated them as less socially competent, they were satisfied with their social lives. Suzigan et al. (2011) concluded that TS girls have normal social knowledge but they do not use it because of other factors, like social anxiety or shyness.

Qualitative research on patients' experience

There are some qualitative studies that have focused on the patient's point of view. These studies could be very useful in order to make some hypotheses about the

interplay of different variables in TS, and to attempt a more complex explanation of psychosocial functioning in these individuals.

In an interesting study, Sylvén et al. (1993) interviewed 22 late-diagnosed middle-aged women (median 17,5 y). The authors reported many problematic issues, above all infertility which brings the fear of not being accepted, a complicated sexuality and relationships with men. Moreover, the information received about it was insufficient for most women. Most of them found out about it thanks to doctors, two of them by themselves. The fact that the cause of TS is a chromosome aberration contributed to the perception of the syndrome as a serious condition. The subjects interviewed reported that they isolated themselves as they felt different from their peers because of delayed puberty; height and excess weight were major problems but no correlation between body height and psychosocial issues was found. Many women have discontinued HRT. Most of them were satisfied with their present life, but reported many difficulties and sorrow in getting there.

In a qualitative research study on 97 TS individuals aged 5 to 59, Sutton et al. (2005) found that, regardless of age, infertility was the most frequently cited concern, followed by short stature, sexual development and general health. Sutton et al. (2006) found that 30% of 97 TS subjects mentioned spontaneously that their healthcare providers or parents had withheld all or part of their diagnosis. Okada (1994) also mentioned that none of the Turner women included in his study were informed about the details of Turner syndrome. Sutton et al. (2006) found that individuals reporting secret-keeping were more likely to have had a negative perception of the health care providers' role in the process of diagnostic acknowledgment. Suzigan et al. (2004) reported that 42% of 36 TS women were unable to explain the etiology of TS.

Another qualitative study by Kagan-Krieger (1998) has shown two factors influencing the coping style in TS. One of them is family (in particular, how family members accept the diagnosis within the family context), the other is self-esteem and the number of additional resources the subject can count on.

One research study (Starke, Albertsson-Wikland, & Moller, 2002) has focused on the

parents' experience of receiving the TS diagnosis. The process of diagnosis was affected by who initiated the investigation: those parents who had not initiated the investigation were more shocked and more often failed to comprehend the information given by doctors.

These studies seem to have anticipated many important findings of later quantitative studies, such as the fact that delayed puberty has negative consequences (Sylvén et al., 1993) and the importance of the infertility issue (Sylvén et al., 1993; Sutton et al., 2005); that stature is not the biggest problem, and that weight is important for psychosocial adjustment (Sylvén et al., 1993; Sutton et al., 2005).

3 THE THIRD PERSPECTIVE: STUDIES ON DETERMINANTS OF PSYCHOSOCIAL ADJUSTMENT IN ADULTS WITH TURNER SYNDROME

Although the picture I have collected shows impaired psychosocial adjustment in the TS population, the reasons for these social difficulties are still undetermined. There are several possible explanations from a theoretical point of view and the issue has been discussed in literature: the social difficulties could be secondary to deficits in social cognition, especially with facial affective processing (Hong et al., 2009) or due to social anxiety (Suzigan et al., 2011). They could be secondary to a strategy for coping with short stature, TS features, infertility issues; they could be due to genetic or hormonal factors. On the other hand, more probably, there could be a complex explanation which includes all these factors. It could be useful to describe their interplay and their different roles in order to make decisions about the clinical management aimed at facilitating the social adjustment of TS patients from childhood. Unfortunately, only few studies were able to identify specific determinants of positive or negative outcomes using correlation and regressive analysis, while most of the research simply provides a picture of social adjustment in this population.

I shall review and discuss the factors that have been indicated as determinants of social adjustment in these few studies.

Pubertal management and oestrogen therapy

Paediatric management of patients with Turner syndrome focused on height, frequently resulting in a delay of pubertal induction. Taipale was the first, in 1979 in a study based on clinical intuition, to identify suffering caused by entering adolescence without the onset of pubertal development. Later on, Sylvén et al. (1993) also described this danger as connected with delayed puberty.

Carel et al. (2006), in their famous population-based cohort study on 568 young adult women with TS, found that pubertal management clearly influences psychosocial adjustment and sex life in Turner syndrome individuals. The authors concluded that delayed induction of puberty had a long lasting effect on social and sexual life and that pubertal induction should be started at a normal age. This recommendation has been included in the guidelines of TS clinical management.

As regards HRT, the data is not clear yet. Pavlidis et al. (1995) found that the women who were taking HRT scored significantly higher on body image than the ones who were not. Ross, Roeltgen, Feuillan, Kushner, and Cutler (2000a) found that oestrogen therapy in young girls with TS was significantly associated with improved verbal and non-verbal memory. This was done by comparing an oestrogen-treated group of pre-adolescents with TS to a placebo-treated one.

The study on oestrogens highlighted the hypothesis that there is a window of time (during the pre-adolescent period) in which exposure to oestrogen has significant effects on TS individuals.

An important finding is that, despite the evidence of its importance, a large number of women with TS declined oestrogen therapy in adulthood (14.5 % in Verlinde et al., 2004; 20% in Sheaffer et al., 2008; 40% in Sylvén et al., 1993).

Weight

Both Lagrou et al. (2006) and Carel et al. (2006) found a correlation between health status and excess weight.

Height and Growth Hormone therapy

There is no consensus in the literature as to whether short stature by itself should be considered a risk factor for psychosocial and social functioning.

Growth-promoting therapy with GH has been given in cases of TS since the 1960s, and has been combined with growth hormone since the mid 1980s. Several large-scale clinical trials have shown good results on final height (Nilsson et al., 1996).

The main research on social adjustment found that height (Lagrou et al., 2006; Okada, 1994) and height gain due to GH treatment had no effects on social adjustment outcomes (Carel et al., 2006); the authors concluded that height does not have a significant impact on psychological functioning.

In 2007, Baxter, Bryant, Cave, and Milne developed an accurate meta-analysis of the effects of GH therapy, excluding all the non methodologically valuable studies, and concluded that existing evidence seems to indicate that growth and final height can be improved in TS. The author argues that the more pressing question now is the cost-effectiveness of such treatment, to which he replied pointing out two elements for further research:

1- A good measurement of clinical effectiveness could be based upon a comparison between randomised groups of patients receiving or not receiving GH treatment. This could prove impossible, however, since it would be ethically difficult not to treat these girls with GH.

2- A full consideration of the cost and benefits of GH treatment for TS should include not only effects on height, but also other outcomes, such as psychological or cognitive effects, which in the past have received little attention in the evaluation of GH in TS.

In this review I agree with Baxter et al when they suggest that, especially, if compared to other fields of research into TS, the relationship between GH therapy and psychological outcomes is poor and that, when this relationship has been considered, there is important methodological reserve, especially in terms of conflict of interest.

The Canadian randomized controlled trial (Rovet & Holland, 1993) on GH therapy's effects on psychological adjustment indicated positive effects on social competence and self-esteem. Similar results were described by Huisman et al. (1993) in a trial on 38 Dutch girls with TS. The first studies stressed the negative role on psychosocial adjustment of unrealistic expectations about the effects of the treatment on growth. The last findings have been confirmed in a French study (Carel et al., 2005).

Recent research studies on young TS women who reached normal height and had age-appropriate pubertal development reported normal HRQoL (Bannik et al., 2006; Lagrou et al., 2006). The authors hypothesize that GH and oestrogens positively influenced HRQoL in young women with TS.

Sheaffer et al. (2008) found that height was a predictor of social adjustment in their study on relatively old patients who did not receive GH. This data could point to the hypothesis that GH treatment, which significantly reduces the stature problem (since the gain is collocated in a very important range of height, boosting it from an average of approximately 140 cm to an average of approximately 150cm), decreases the importance of issues connected to short stature compared to others, such as fertility. Considering the frequently small and heterogeneous samples used until now (except in the Canadian and French cases), more studies are needed in this area of research.

Dysmorphic features

Unfortunately, most research has not included this variable in the number of potential determinants of outcome measures. However, the studies which did are consistent in reporting that this aspect of TS is not related to social adjustment.

Aran et al. (1992) found that positive adjustment in professional and social areas were not related to physical stigmata. Schmidt, Rubinow, and Bondy (2006) found that neck webbing was not associated with negative psychological symptoms in TS women. Sheaffer et al. (2008) examined physical stigmata as a factor that might influence sexual function and there was no correlation between the two variables. Carel et al., (2006) found that dysmorphic features were not associated with self-

esteem and social adjustment.

Hearing loss

The impact of hearing loss in middle-age has been underlined (Hultcrantz, 2003) and in three important studies it has been identified as a predictor of perceived health related to quality of life (Naess et al., 2010; Carel et al., 2005; Boman et al., 2001). A discordant result comes from Sheaffer et al. (2008): the authors did not find any effect of hearing loss on relationship status or sexual function.

Education

The results regarding this variable are not consistent. Carel et al. (2006) found that the level of education was a strong predictor of health status. On the contrary, Naess et al. (2010) concluded that education was not correlated with health status and argued that education is not as strong a predictor of health status in TS as it is in the general population.

Infertility

Infertility has been described as the major problem for women with TS in all the qualitative studies (Sylven et al., 1993, Sutton et al., 2005; Suzigan et al., 2004), but psychosocial status pertaining fertility issues has not been much examined in this population. An important study by Schmidt, Cardoso, & Ross (2006) comparing 100 TS individuals with normal and with premature ovarian failure individuals, showed the role of infertility as a factor in the anxious, depressed and lower self-esteem profile. Schmidt et al. (2006) compared TS women to POF and to normal women, evaluating shyness, anxiety and social anxiety, cognitive profile (IQ), visual-spatial abilities and perceptual difficulties. The authors found that none of the cognitive variables correlated with any aspects of psychosocial dysfunction, suggesting that shyness and social anxiety experienced by adults with TS are not related to neurocognitive deficits due to chromosome deletion. They concluded that the similar

response in POF and TS women suggests that the common experience of ovarian failure is the major determinant in their psychosocial phenotype.

4. STUDIES ON PSYCHOLOGICAL INTERVENTION

Very few studies have described psychological intervention in TS, and they all focus predominantly or solely on childhood or adolescence. Only few have evaluated its effectiveness (Williams, Richman, & Yarbrough, 1992). This field needs much more extensive research but in this section, these findings are nevertheless presented.

Recent evidence has proven that focused cognitive interventions, such as structured maths training programs, may significantly improve behavioral performance and functional brain activation in girls with TS (Kesler, Sheau, Koovakkattu, and Reiss, 2011). This provides direction for the development of neurocognitive treatments that are more TS-specific in the future.

Individual psychotherapy which focused on information about the diagnosis has been reported but not evaluated (Watson & Money, 1975). Support programs for the individual and her family have been described by Mullins, Lynch, Orten, & Youll (1991). The authors put emphasis on the emotional and informative needs of these families. They reported good results on a clinical basis.

Loughlin (1993) used groups of dance therapy with both teenagers and adults; the evaluation of the intervention was made on a clinical basis but was positive. Williams et al. (1992) describe an experience of training in problem-solving strategies where pre-test and post-test performance differences in parallel forms of a visual-spatial orientation task were examined. The group of TS girls showed significant improvement in visual-spatial task performance after the training.

Chadwick, Smyth, and Liao (2014), describe a 1-day psychology workshop targeting problems of self-esteem in women diagnosed with TS. The workshop drew on cognitive-behavioral therapy and narrative therapy skills and emphasized increased self-awareness of interpersonal difficulties and improved capacity for self-management. The intervention improved RSS and HADS scores at 3 months.

Starting from the more recent guidelines for TS management (Bondy, 2007), many articles on care for TS patients mention the value of patient support groups and the utility of psychological support (Saenger et al., 2001; Kesler, 2007), but no evaluation has been reported.

Some authors (Kesler, 2007; Hong, 2009) suggest that research in this field should try to develop syndrome-specific interventions, critical for improving the quality of life in individuals with TS.

METHODOLOGICAL ISSUES

Finally, from this review of the literature on psychological aspects of TS, I would like to point out some methodological consideration for further research.

Most of the research in this field in fact offers a picture of the social adjustment in this population; only few studies tried to identify the determinants of positive or negative outcomes using correlation and regressive analysis and they have typically involved relatively small sample sizes, large age ranges and mixed genotypes. I notice that this field of research lacks a common theoretical frame.

About the subjects

Regarding the subjects' selection, there are some problems generally connected to the study of a relatively unusual medical condition:

- ✓ Most of the studies have small samples: the population-based cohort study of the French group of Study on TS (Carel et al., 2006; Carel et al., 2005) is the only one which has a large sample (N=568);
- ✓ Results are often presented for a sample with a wide age-range without sub-division. Moreover, in the TS population, the clinical management of the medical condition has changed significantly in the last 15 years, and younger subjects are more likely to have received GH treatment and pubertal induction at a normal age than older subjects are.
- ✓ Regarding the selection of the subjects: the source of recruitment can

influence the results. Sources could be medical, paediatric, or endocrine clinics; genetic clinics; patient support organisations; the register of GH therapy. The individuals are included in studies on the basis of their informed consent. Ethical issues should be considered; therefore it is not possible to reach all TS individuals and do randomised sampling: all the studies used self-selected samples. In addition, few studies are clear about the selection of the participants and information on the ones who were not reached or refused to participate is not always available. These considerations mean potential bias in a variety of domains. Individuals with more pronounced problems or with better psychosocial adjustment can be over-represented. Few studies are explicit about having excluded, or not, individuals with mental retardation.

✓ In some studies the data on medical history is extracted from medical archives while in others they are self-reported by patients. This makes it difficult to rely on this second study group's results.

✓ The most common karyotype in TS is 45,X0, meaning that the second sexual chromosome is absent; some individuals have a combination of complete karyotypes and karyotypes with only one sexual chromosome (mosaicism 46XX or 46XY and 45,X0); some others can have different abnormalities of the second X chromosome. The selection criteria of TS subjects are often unclear regarding the karyotype. The clinical practice guidelines (Bondy, 2007) state that the diagnosis of TS requires the presence of some characteristic physical features in phenotypic females coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism: individuals with 45X cell population but without clinical features are not considered to have TS. Many earlier studies did not have proven evidence of these karyotypes in TS diagnosis. Moreover, phenotypical and medical implications of TS can vary a lot: Turner features (webbing of the neck, low-set ears and hairline, cubitus valgus) may occur to varying degrees. Most of the studies reviewed accurately did not take all of these differences into account.

- ✓ Owing to the difficulties in recruitment described above, it may happen that different studies are conducted on the same subjects at different times. We should consider an experimental effect.

One or more of these sources of bias will be common to most of the research in this field.

About the comparison method

Many studies on the psychological aspects of TS relied upon normative data of the reference population. Some studies compared the TS sample with an age-matched female sample, but since these groups differ significantly in height, ovarian function and neurobiological function, the importance of these different factors cannot be assessed.

Some research used constitutionally short-statured female subjects as a comparison group in order to investigate the role of final height. Few studies compared TS subjects with their sisters. Only very few studies were designed to assess the roles of different factors using more than one comparison group including a group of karyotypically normal women and another composed of females with fragile X syndrome or karyotypically normal subjects with either spontaneous premature ovarian failure (POF) or short stature.

About the instruments used

Most studies use generic questionnaires with ad hoc questions, but these standardised questionnaires vary from one country to another, thus are often not comparable.

Cultural issues

When we compare studies on social adjustment conducted in different countries, cultural influences should be considered.

CHAPTER 2

A RESEARCH PROJECT.

ADULTHOOD WITH TURNER SYNDROME: QUALITY OF LIFE, PSYCHOSOCIAL ADJUSTMENT AND CLINICAL MANAGEMENT IN 70 ITALIAN WOMEN

In this chapter, I will present the research project I have developed in the past three years. The project of this study was designed alongside the everyday experience of the Unit for Rare Disease. We thought it would be useful to primarily focus on adulthood: we wanted to know how their adulthood was and we hoped to find, from the experiences of people who have grown up with TS, valuable information to enable us to take better care of newborns. Methodological issues and ethical concerns were then considered. In addition, I had to adapt the project to the organisation of the Unit and to the complexity of the follow-up of the adults with TS. Finally, the research project was submitted to the Ethics Committee of the Bologna University Hospital and was approved.

OBJECTIVE AND AIMS OF THE STUDY

This research aimed to delineate the Quality of life (QoL) and the psychological and socioeconomic adjustment and to investigate the clinical management and the experience of Italian women with TS. We also wanted to explore the relationships between clinical management and general psychosocial adjustment and QoL to develop the best way of taking care of this population. Thus, we decided to assess many different variables, among those, ones indicated as more relevant by previous studies, to try and make some hypothesis on the way they interact in TS.

METHODS

Participants

Seventy adult females with TS were enrolled [mean age years: 27.8 ± 7.6 ; range 18-48 years]. Genetic diagnosis was available for all participants.

Comparison group

Data collected from people with TS were compared with those of a group of women matched by age and educational level [n = 70; mean age: 27.9 years, ± 7.3 , range 21-48 years], who had no historical or present medical conditions. The women included in the comparison group were recruited among medical, nursing and welfare staff at the Paediatric Clinic of Bologna's Sant'Orsola- Malpighi University Hospital and among students of medicine and obstetrics at Bologna University.

Recruitment strategy and data collection

Ethical issues were considered for the selection and it was clear that it was not possible to contact all TS Italian individuals and do randomised sampling. I used a self-selected sample. The source of recruitment was the paediatric Endocrinology Unit at Bologna University Hospital.

A total of 75 individuals more than 18 years old were invited to participate in occasion of the follow-up visit. The only other criteria of inclusion was to have a diagnosis of TS, there were no exclusion criteria. Of those contacted, 70 (93,4%) gave their consent to participate in the study, 5 (6,6%) declined to participate. The participants were asked to answer a self-report questionnaire while waiting for the follow-up visit which comprised of different medical tests during an entire day. Participants were also asked for their permission to use all the data on their medical condition archived in our database including the genetic test performed. The five non-participants were not statistically different in terms of age and karyotype (the consent for the use of their data for research purposes was included in the general consent for sanitary treatment that all patients sign when they accept the adult follow up programme).

Consent

Informed consent was obtained from each participant of both the TS group and the comparison group at enrolment in the study, and as I explained before, the study was approved by the ethics committee for human investigations at the University of Bologna.

Main Outcome measures

Taking into account the ethical issues involved in the research connected to a high level of medicalization of these individuals and the practical difficulties, I planned a single and as brief as possible questionnaire, which included various instruments and some open questions, in order to investigate:

- a. General indicators of psychosocial adjustment:
 - a) Educational background and employment situation
 - b) Sexual life milestones, partner relationships and marital status
 - c) Living situation
2. Social behavior and withdrawal behavior (ASR: Achenbach's and Rescorla's Adult Behavior Checklist for self-report) (22)
3. Psychological constructs:
 - a) Quality of Life (World Health Organization Quality of Life –Whoqol-Bref) (23)
 - b) Depression, anxiety (ASR)
 - c) body concern about body components relevant for turner 's phenotype: shoulders, neck, ears, breast, stature and chest.
4. We also asked the subjects to answer 8 questions about:
 - a. Sexual orientation: we asked them how they consider themselves among a multiple choice (heterosexual, homosexual, bisexual).
 - b. Sentimental relationships: we asked how many partners they had and if they had sexual intercourse.
 - c. Preoccupations connected to having TS: The answers to this question were categorized based on content analysis by three independent judges.
 - d. Information on diagnosis communication:

- At what age they were informed of having TS
- Who gave them the information on TS
- If they were satisfied
- If, in their opinion, the information they received was complete or not

The full questionnaire is reported in the section “Attachments”.

The QoL study was carried out using the World Health Organization Quality of Life (Whoqol) study. The Italian version, OMS, 1998, measures quality of life in terms of four areas: Physical health, Psychological health, Social relationships, Environment. The WHOQOL– Bref is a 24-item questionnaire and provides scores in four domains of perceived quality of life on a 0-100 scale in the four areas, with the higher values indicating a better QoL.

ASR, Achenbach and Rescorla’s Adult Behavior Checklist, provides a standardised description of behavior problems and competencies in adults. This questionnaire is broken down into cross-informant syndromes and DSM-oriented scales. The cross-informant syndromes considered are Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, Aggressive Behavior. The six DSM-oriented scales are Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems and Conduct Problems. This instrument generates a total problem score (TS), which is an index of psychopathological severity. Additional scores of maladjustment can also be estimated from the existing syndrome subscales, and are computed on Internalizing (IS) and Externalizing (ES). ES includes Impulsive Behavior, Conduct Problems, and Aggressive Behavior. IS includes behaviors such as Withdrawal, Somatic Complaints, Anxiety and Depressive Problems. The scores provided by the Instruments are subdivided into 3 ranges: normal range scores (for all scales <64, for TS, IS and ES <60), borderline range scores (for all scales 65-69, for TS, IS and ES 60-63), and pathological range scores (for all scales ≥ 70 , for TS, IS and ES ≥ 64). The Italian version of the

questionnaire was translated in 2000.

The concern about body components was assessed by asking the participants to indicate on a Likert scale (range from never (=0) to always (=5) for a total of 6 points) how much they feel unhappy with the components of their body. I chose the components that are connected to Turner stigmata.

Statistical analysis

All the data were anonymously collected in a database. Continuous data is presented as mean±standard deviation and categorical data is presented as count and percentage.

Psychosocial variables, QoL and ASR scales were assessed in the group of participants and in the comparison group.

The results among the TS group will firstly be presented, then the data from the comparison group and the differences based on age and diagnosis will be given. As regards marital status, education and work, the TS sample will be compared with the general Italian population data reported by the Italian Statistics Institute ISTAT (<http://dati.istat.it>) and EUROSTAT (<http://eurostat.it>)

Chi squared test and Student's t-test or Mann-Whitney tests were used, as appropriate, for group comparisons on other variables assessed. A p value of less than 0.05 has been considered statistically significant.

RESULTS

Karyotype and Turner phenotype

Genetic tests were collected for all the participants: 25 (35.7%) women have a X-monosomy, 11 (15.7%) a X-mosaicism, 26 women have X-structural abnormalities (X-SA) [15 X-isochromosome (21.4%), 9 X-ring (12.9%), 2 X-deletion (2.9%)] and finally 8 (people) have a Y-mosaicism (11.4%). (Tab. 1). The comparisons between different karyotype are not enlightening differences in the most relevant variables.

Karyotype	X-Monosomy	X-Mosaicism	X-Isochromosome	X-Ring	X-Deletion	Y-Mosaicism
Frequency	25	11	15	9	2	8
Percentage	35.7	15.7%	21.4%	12.9%	2.9%	11.4%

Tab. 1: Distribution for karyotype

The mean final height was $151.9 \pm 7\text{cm}$ (range 135.3-169.9) with no significant differences depending on karyotype. Eighteen women have cardiac anomalies, 17 have renal anomalies. As regards the “TS stigmata”, 13 (19.1%) people have no phenotypic signs, only one person has severe TS signs (1.5%), the most of the sample has faint (47.1%) or moderate (32.3%) phenotypic sign of TS. Data is missing for two subjects.

Degree	Frequency	Percentage
Absent	13	19,12%
Faint	32	47,1%
moderate	22	32,3%
Severe	1	1,5%

Tab. 2 Turner's phenotypical signs

Final height, GH and concern about stature

The mean final height of women with TS was 151,86 (ds=7.06). The majority of the sample underwent GH therapy (for a mean time of 79,5 months), only 8 subject (11.8%) didn't had the therapy, the data is missing for two subjects. The women with TS are significantly more unsatisfied of their stature than the women in the comparison group. ($p=0.0001$). 32.3% declared to hate the stature from sometimes to often. Satisfaction with stature do not correlate to final height.

Age at diagnosis

Mean age at the moment of the diagnosis medically registered was 9.4 ± 5.2 years (range 0 – 32). The mean age at which the women received the communication of the

diagnosis is 13.3 ± 7.1 (range: at birth to 32 years) but 11 participants did not respond to this question, and one girl responded that she always knew.

Social, work and educational level

35.5% of the women with TS of our sample were students, of them, a portion studied and worked at the same time (8.5%), 17.4% of the women enrolled had a degree. Among the students and people with degrees, 46.1% were in a humanities discipline, 5.1% in law and economics disciplines, and 38.5 % in a scientific subject. 36.6% were employed; of these 76.9% had a desk job with medium-low income, 19.3% of them were employed in cultural occupations (teacher, professionals). The remaining 16.9% of the sample was unemployed and searching for a job. The occupational level of our sample (36.6%) was significantly lower than that of the 15-65 year old Italian females (50.5 %) (eurostat.it). Possession of a university degree was the same than in the general Italian population (17.4% versus 17.5%) (eurostat.it).

Civil status

Most of the women with TS (75.4%) lived with at least one parent, 2.9% lived alone, 8.7% with housemates. Only 13% had a new family (partner, husband), whereas the figure among Italian females aged 20-60 years was 56.2% (Istat.it). Only seven individuals of our sample were married or living with a partner; none were separated or widowed. This information was missing for one participant. Only four women were mothers: one woman was the mother of adopted children; one had biological children; two underwent heterologous artificial insemination and succeeded in having children.

Gender identification, sexual orientation and love relationships

Regarding sexual orientation, 67 women answered the question, 66 of them declared they were heterosexual, only one homosexual; the sample of women with TS is not significantly different from comparison group.

Regarding the question: “How many love relationships have you had till today?” in our sample of women living with TS, 5 people (7.1%) did not answer, the remaining 65 women are significantly different from the women of the comparison group ($p=0.0001$). From the TS participants 52.4% replied to only having had one love

relationship, 43% had two or more relationships; three people (4.6%) responded that they have never had any love relationship. As regards the question if they have ever had sexual intercourse, 18.6% of the sample did not respond. Among the remaining, only 29.6% declared to have had sexual intercourse, significantly less than the 85.2% of women in the comparison group ($p=0.0001$).

Pubertal induction and hormone replacement therapy

Fifty-seven women were on HRT ($n=60$, 88.2%). 20 women (28 %) of the sample had B2 spontaneously at a mean age of 12.6 ± 2.5 years (range 7.5-15.7). The starting age of HRT with estrogens occurred at the mean age of 15.8 ± 2.3 years (range 10-24 years). 17.1% (12 people) have spontaneous menarche. Seventeen of the 20 women who had spontaneous B2 started HRT with oestrogens at a mean age of 16.9 years \pm 3.4 years.

Diagnosis communication

Among the participants only 53 responded to the question about who informed them of their diagnosis: 35.8% declared they were informed about their clinical condition by the doctors; 28.3% by their parents; 11 women (20.7%) were informed by both parents and doctors; 3 (5.7%) people declared they got the information by the internet and 5 (9.4%) said they had to search for information on their own. The questionnaire provided an open blank space under this question for any comments the women felt they wanted to write on the diagnosis communication and five of them underlined they perceived there was something to conceal and they felt the need for more information. As regards the completeness on the information, for 25 women from the 45 responders (55%), the information they received was incomplete. Finally, 53 replied to the question on satisfaction about diagnosis communication: 31 women (58.5%) were unsatisfied about the way they were informed, 22 were satisfied. The women satisfied of the diagnosis communication were more often informed by their parents (73.3%), while the unsatisfied women were more often informed by the doctors (78.95), more often, the unsatisfied women were the ones who found the information about their diagnosis by themselves (87.5%) ($p=0.004$). (Tab. 3)

DIAGNOSIS COMMUNICATION	In your opinion, were you satisfied with the way you were informed of your diagnosis?		X=13.07 P=0.004
Source	unsatisfied	Satisfied	Total
doctors	15 78.95%	4 21.05%	19
parents	4 26.67%	11 73.33%	15
both	6 45.45%	6 54.55%	11
self-discoverers	7 87.50%	1 12.50%	8
Total	31 58.49%	22 41.51%	53

Tab. 3 Source of communication and satisfaction

Preoccupation about TS

Sixty people answered the question “In your opinion which are, if any, the main problems connected to living with TS?”. Five of these responded they do not have any problems with living with TS. Two judges performed content analysis on the 60 answers independently, then the two judges individuated 6 categories of preoccupation (Tab. 4) and assigned in common agreement at least one code to any answer collected. One subject could express more than one preoccupation and received more than one code. The first problem in line is “to be unable to have children” (32 people on, 53.3%). For 15 people, this is the only worrying thing of living with TS, the second problem, pointed out by 17 women (28.3%) from our sample is “feeling different in some way from other women”, in third position (21.7%) there is “the preoccupation for health in the future”, then the “fright of being rejected by a partner for being infertile” (11.7%). Only five subjects (8.3%) are worried about “being of short stature” and for all of them the short stature was not the only preoccupation mentioned.

Categories	Percentage	Frequency
'Impossibility of having children'	53,34%	32/60
'Feeling different/less than other women'	28,34%	17/60
'Problem of health in the future'	21,67%	13/60
'Being accepted by a partner'	11,68%	7_60
'Short stature'	8,34%	5_60
'No preoccupations'	8,33%	5_60

Tab. 4: Preoccupation in living with TS. Ten individuals did not responded.

Body concerns

As regard the satisfaction with stature I gave the result above, for the others body components included in the study, the women with TS are generally satisfied with their ears, necks, of the breasts, of their genitals, and of the chest and the shoulders. On this issue, they are not different from the women in the comparison group. The satisfaction with these body components does not correlate with the degree of Turner stigmata.

QoL

The present sample of women with TS showed good QoL. Mean scores were over 50 in all four evaluated areas, although the score in the psychological area was the lowest one [54.2 50-58.3] (Tab. 5).

	TS group Median [25° – 75°]	Comparison group Median [25° – 75°]	p
Physical area	78,6 [71,4-83]	75 [67,9-78,6]	0,0279
Environmental area	65,6 [56,3-68,8]	59,4 [46,9-68,7]	0,0291
Psychological area	54,2 [50-58,3]	58,3[54-62,5]	0,058
Social area	62,5 [50-75]	75 [58,3-83,3]	0,021

Table 5: WHOQoL median scores and interquartile range in the groups of women with TS and in the comparison group.

The most satisfying area was the physical one, with a median score of 78.6 [71.4-83] points. The comparison group had a significantly lower QoL in the physical and environmental areas, while showing a significantly better QoL in the psychological and social areas.

ASR scales

The median and interquartile range scores of the eleven ASR scales of people with TS and women in the comparison group are summarized in table 6. The women with TS had a median score in the borderline range for anxiety, depression and withdrawal behavior, which resulted significantly higher in the sample population than in the comparison group (p=0.016; 0.018.).

ASR SCALES	TS group Median [25° – 75°]	Comparison group Median [25° – 75°]	≥ 65 in TS group (%)	≥ 65 in comparison group (%)	P
Anxious and depressive symptoms	60 [53-66]	52 [50-56]	30,99	14,08	0,016
Withdrawal behavior	59 [50-65]	51 [50-53]	32,39%	15,49%	0,018
Somatic complaint	51 [50-58]	54 [01-60]	12,68%	18,31%	0,354
Thought problems	51 [50-55]	51 [50-54]	7,04%	5,63%	0,731
Attention problems	57 [51-60]	56 [50-59]	14,08%	8,45%	0,288
Aggressive behavior	54 [52-61]	52 [51-55]	14,08%	12,68%	0,805
Rule breaking behavior	51 [51-55]	51 [50-55]	2,82%	4,23%	0,649
Intrusive behavior	50 [50-54]	51 [50-56]	2,82%	4,23%	0,649
Internalizing (IS)*	58,5 [48-65]	52 [43-57]	40,58%	7,25%	0,001
Externalizing (ES)*	52 [45-57]	48 [47-55]	8,45%	9,86%	0,771
Total problems	53,5 [45-59]	51 [44-53]	14,08%	7,04%	0,172

Tab. 6 ASR: Median scores and interquartile range for the group of individuals with TS and the comparison group. Percentage of borderline or clinical scores (considered as greater than 65, or than 63*). P for comparison of percentages of borderline or pathological scores.

Taking into account the individuals who had scores ≥ 65 (borderline for clinical relevance) (Achenbach & Rescorla, 2003), 22 individuals (31%) resulted borderline or pathological for anxiety and depressive symptoms and 23 women (32.4%) for withdrawal behavior. The individuals with a total score of more than 63 (with a borderline significance, Achenbach & Rescorla, 2003) were 28 for IS; 5 for ES and 10 (14.0%) of the sample had a score of > 65 on the total problems scale.

CHAPTER 3

DISCUSSION AND CONCLUSIONS

In this last chapter I will at first discuss the main results and then I will draw some conclusions from this research and the review of the literature on psychological aspects of TS.

DISCUSSION

Karyotype and psychological outcomes

Comparisons between the different karyotypes for the most relevant psychological variables (anxiety and depression, withdrawal, internalizing behaviour, QoL) were performed and no differences were enlightened.. We have to consider that we have small subgroups and maybe our data is not reliable. Anyway, this finding could indicate that the genetic component is not the main determinant for such complex behaviours.

Quality of life and social adjustment

The study presented in this thesis suggests that individuals with TS have a good QoL. Especially as regards the physical area, women with TS displayed higher scores than the individuals in the comparison group. This interesting result could be explained by the feeling of being well cured and under control, due to the complex follow-up carried on by these women in adulthood. Or, it could be a sign of denial of the concern about their health. A third way of explain this finding could be that women with TS have different internal references (Bannik et al., 2006).

The results in the ASR scales indicate that women with TS are psychologically in the normal range, however, compared to the comparison group we have to notice that TS seems to have an influence on the psychological functioning: anxiety, depression, withdrawal and internalizing problems. These are enhanced in the group of women

with TS compared to the comparison group.

TS also seems to have an effect on the socioeconomic status: this sample of women with TS achieved the same educational level but are less engaged in work compared to the age-matched general Italian female population.

Our women with TS have a lower perception of QoL in the social area than women in the comparison group. Many previous studies have found that TS women have limited social lives, perceive themselves as less socially competent (Lagrou et al., 2006) and have deficits in social cognition; many studies have reported that they nevertheless seem to be satisfied with their social lives (Aran, 1992; Suzigan et al., 2011; Bannik et al., 2006; Sylvén et al., 1993). Furthermore, in some research on TS, a tendency to minimize impairment issues, even self-reported ones (Aran et al., 1992; Sheaffer et al., 2008; Lagrou et al., 2006; Suzigan et al., 2011), can be found. Many authors suggest that TS women attempt to show that they are better and more adapted than they really are (Delooz, 1996; Lagrou et al., 1998; McCauley et al., 2001; Suzigan et al., 2004). Delooz et al. (1993) found defensive and denial attitudes in 70% of the women interviewed. Some authors argued that the feeling of satisfaction with their social lives could be due to impaired social reading (Suzigan, 2011; Hong et al., 2011). Women with TS interviewed in the present study seem to be aware that the social area is less satisfying for them. Recently Lepage, Dunkin, Hong, and Reiss (2012a) suggested that executive dysfunctions play a role in social impairments encountered in TS, but also that some specific aspects of social behaviour are altered beyond what can be attributed to cognitive difficulties in this population.

In the attempt to better understand the social profile in TS, I think we should consider the information coming from clinical experience and from qualitative research: the fact that many women with TS included in this study pointed out the preoccupations of being infertile or different from other women could support the hypothesis that the tendency for social withdrawal should be interpreted as a coping strategy for a perceived social impairment (due to infertility and/or to cognitive disabilities and/or to short stature and /or for the consequences of feeling “sick” or

“different” for being so medically controlled). Further research in this direction is needed in order to address the question of whether women with TS and deficits in cognitive abilities are the ones who gain late autonomy or have fewer or later partner relationships. Or, perhaps, if the impairment in social reading has a role, are these the women who are most satisfied with their social lives?

Finally TS affects the sentimental life: a lower percentage of woman with TS was married or in a stable relationship and a higher percentage do not have an active sexual life. In my opinion this aspect of living with TS has to be carefully discussed. Since we did not find any differences connected to being under HRT, we could hypothesize this impaired sentimental life is not due to hormonal effect, at least in adulthood. Schmidt, Cardoso and Ross (2006) suggest that the experience of ovarian failure could be the major determinant in the TS psychosocial phenotype. However, the interplay of infertility with the impairment in social cognition and in emotion recognition (Lapage et al., 2012a, Hong et al. 2014) needs to be better clarified. Moreover the issue of sexual functioning also remains to be understood: considering the data on HRT, we could say that lower sexual activity does not seem to correlate with endocrine factors in adulthood but we can't exclude a relevant role of hormones in adolescence. Many of the women with TS in our sample declared to be frightened of being rejected by a man. All these factors are probably connected. My clinical experience lends me to think the crucial period is the adolescence: the way a girl works through the painful acknowledgment of being infertile is very important to her future sentimental life and this challenge often arrives in the time the girls with TS are dealing with an anomalous pubertal development. The challenge of accepting the HRT without developing a feeling of “inferiority” and “abnormality” has been underestimated until now. In my opinion there is another variable determinant which has been underrated too: how parents have conceived the information of their daughter being infertile affects how a girl lives the anomalous pubertal development and the infertility issue. Finally an overprotective parenting style, prohibiting a natural childhood, could be another useful factor in explaining the impairment in the sentimental and social life of these women.

Stature and final height, body components and Turner's stigmata

As I already mentioned, stature plays a central role in the clinical management of TS. There is also a rich and contradictory literature trying to investigate psychological consequences of shortness. From the study of Carel et al. (200) onwards it became clear that it was important to assess the effects of GH therapy in women with TS. We know that it is an expensive and demanding therapy, the purpose of which was once given for granted, nevertheless in recent years it has been the subject of reflection. We felt it necessary to include, among the variables needed to evaluate the effects of GH therapy, the satisfaction perceived by women with their stature and to compare it to the height actually reached. It seems that stature is a source of uneasiness for women with TS: many of them are perceived significantly less satisfied with their stature than women in the comparison group. It has been very interesting finding that, in our sample, the satisfaction with stature and actual height did not correlate: on the basis of this result the satisfaction seems influenced by factors other than the actual physical appearance. We can assume that self-esteem and self-acceptance are playing a part in it. This finding raises, in my opinion, important questions about clinical management of these patients. My clinical experience suggests to me that there may be complex psychological effects associated with taking a therapy that is supposed "to make you grow" and that implies being measured every three months. This could lead to some negative aspects: focus of attention on stature, the creation of false expectations and the disappointment of having to use medication to obtain height while others succeed naturally.

Diagnosis communication

The results from the diagnosis communication questions show that women with TS preferred to receive information from their parents. I think this is a very important issue that brings ethical and cultural problems to the surface. In Italy the traditions of family, a less than advanced equal opportunity culture and prejudiced ideals regarding sexual taboos constitute significant barriers to open parental communication about infertility caused by TS. Not infrequently parents prefer that the doctors are the first to discuss this information and sometimes seek to conceal it

from their daughters. I believe it is vital to develop strategies that facilitate the processing of pain by the parents and their ability to speak and communicate with their daughters about the various implications of Turner syndrome.

Limits of the present research

The major limit of this study was the relatively small sample size and the even smaller subgroups for statistical analysis. In addition, the participants were volunteers, representing a selected sample. This approach raises some problems in terms of generalizing our findings for the entire population of females with TS.

CONCLUSION

From the review of literature and from our study described in previous chapters, the following conclusions can be drawn.

1. Indications for the psychological management of this population:

The most recent guidelines of the Turner syndrome consensus study group (Bondy, 2007) include a paragraph entitled “psychological and educational issue” in which several suggestions are made:

1. Psychological intervention to reinforce and support the individual's self-esteem,
2. A comprehensive psycho-educational evaluation immediately preceding school entry or at the time of TS diagnosis.
3. The opportunity to address the ramifications of TS diagnosis, especially infertility, in adolescence.
4. Focus on preparation for the transition to living independently, starting in adolescence

I also suggest:

- b. Counselling to address hearing loss, when present, in order to encourage the

use of a hearing aid (patients are often embarrassed about using this kind of aid and of asking people to repeat what they have said).

- c. Counselling to inform those with TS – and their parents, if necessary – about what TS diagnosis entails especially with regard to infertility and sexual development from preadolescence.
- d. Counselling focusing on diagnostic acceptance in parents from the time of diagnosis in order to: identify feelings of guilt and help parents work through these feelings; promote open communication about diagnostic issues in the family; and finally in order to avoid overprotective parenting.
- e. The literature reports a good quality of life in the TS population, but many pregnancies where there is a prenatal diagnosis of Turner syndrome are currently terminated (Baena et al., 2004). Therefore, more attention should be paid to prenatal counselling in order to provide prospective parents with better and more balanced information. The clinical spectrum of TS is much broader and often less severe than it is described in many textbooks and on the internet.

Our data supports the conclusion that impairments in the social area and in the sentimental and sexual life are the chief negative outcomes of TS management. The capacity of health care staff to address the health needs of children, adolescents and adults with TS properly, and to interact in an open way by speaking clearly to parents right from the moment of diagnosis communication onward may improve the long-term outcome, leading to less need for specialized individual interventions. Increased action of patients' associations and support groups may be an additional key factor. These associations offer the possibility for people who have lived in an isolated dimension for a long time to meet people with the same conditions and discuss any aspect of the experience of living with a rare condition. This empowers individuals to make decisions about their own health and helps overcome the experience of secrecy and loneliness that these women often go through.

I recommend that all adults and children with TS and their parents should be offered psychological support and counselling. Alongside the traditional models of

individual psychological care, I would suggest group therapy, collaboration with support groups, working with groups of parents, and encouraging the multi-professional team to adopt an integrate approach which tries to address the communication among families on the several aspects of TS and gives an appropriate space to the psychological sphere.

2. Indications for paediatric management from the research on social adjustment in TS:

- a. It seem necessary to induce puberty at a physiologically appropriate age in order to enhance self esteem, social adjustment and sexual activity (Carel et al., 2006, Naess et al., 2010). This means it is important to try to avoid delayed diagnosis.
- b. Given the importance of hearing loss as a determinant of social adjustment in TS, more importance should be given to otological problems in childhood and to the prevention of their long-term consequences in adulthood.
- c. Attention should be paid to the risk of excess weight and to preventive measures to avoid it.

3. Open issues warrant for further research

1. The gap between competence and satisfaction with social life:

Further research should address the question whether the tendency for social withdrawal should be interpreted as a coping strategy for a perceived social impairment (due to infertility and/or to cognitive disabilities and/or to short stature) or if it could be due to impaired emotional recognition.

Only one study (Schmidt et al., 2006) has considered both social adjustment indicators and cognitive functioning (IQ, executive function, Emotional reading), and compared different groups of subjects to TS individuals.

2. Social adjustment, infertility and sex life

Schmidt et al. (2006) argue that infertility could affect psychosocial functioning in at least two ways: firstly, hormonal deficiency might have an impact on the brain regions involved in affect regulation and social behaviour; secondly, experiential

factors associated with loss of fertility may have an impact on a woman's self-concept and perception of her role in relationships.

It has been argued that fertility treatment could improve the quality of life of individuals with TS but the psychological aspects of in vitro fertilization have not been studied in this group of patients.

3. Determinants of social adjustment:

The study presented in this work encourages us to consider diagnosis communication and psychological factors as important variables in adults with TS. There are some variables revealed by qualitative research that could be important to consider in further quantitative studies as possible underrated determinants of social adjustment: some diagnosis issues such as physician-patient communication; age of diagnosis; giving information and keeping secrets in the family (Sylvén et al., 1993; Sutton et al., 2005; Sutton et al., 2006); the need for information on sexual development and sexual functioning (Sutton et al., 2005); the perception of illness, especially regarding genetic implications and connected feelings of guilt in parents; the importance of the relationship with the mother for the development of the full female identity (Sylvén et al., 1993; Sutton et al. 2005); HRT compliance in adulthood (Sylvén et al., 1993); the role of impaired self-esteem and of feelings of inferiority connected with being teased by peers (Sutton et al., 2005); the differences between TS individuals who have spontaneous menarche and those who need pubertal induction (Sylvén et al., 1993).

4. Prenatal diagnosis

Since the diffusion of prenatal screening procedures, most of the individuals with TS have been diagnosed while in the uterus. This involves an important change in clinical practice: the communication of the diagnosis to parents takes place in a very delicate moment as we are taught by a certain psychological literature (Engels, Leuzinger-Bohleber, Tsiantis, 2008), when the unborn child is the object of fantasies that are going to deeply influence its future development. The fallout of the challenge of being confronted with the choice of whether or not to carry the pregnancy to term, the differences in processing the diagnosis at this stage rather than later, in my

opinion constitute new and significant variables that should be the subject of research in the coming years. I wonder if the experiences of girls diagnosed at this stage are more favorable or not and what the main psychological challenges and their possible preventive interventions in this new scenario are.

5. Other psychological aspects to be considered:

The negative side-effects of treatment are linked to anxiety over medical interventions. No study has taken these aspects into account.

The parent-child relationship and parenting style when a rare disease is implied are important issues. Since many adults with TS delay leaving home or never leave at all, it could be important to better understand the family functioning of TS individuals. The interaction between parents and children with TS is obviously important for the latter's psychological development, and it is extremely interesting to explore the variations in psychological functioning in this group. There are no systematic studies on parental reactions to TS diagnosis and on the influence of family functioning on individuals with TS. More studies on childhood are needed in order to investigate parenting style, especially regarding GH therapy, and the rate of compliance to it. The issue of acceptance of the diagnosis by parents, and the relationship of this factor to TS girls' self-esteem, also needs to be addressed.

Since prenatal diagnosis of TS is becoming the most common scenario, it could be useful to explore the role of a chronic genetic illness diagnosis at the beginning of the parent-child relationship. Two studies (Lagrou et al., 1998; Rovet & Holland, 1993) describe an increase in family functioning during GH treatment and Van Pareren et al. (2005) found improved family functioning after GH treatment. This data may indicate that the past medical problems of these women and their families have resulted in a greater involvement of the parents in their daughters' lives. This could be an important point to be addressed in the psychological management of this condition. Counselling for parents in order to deal with GH therapy problems in childhood could be important in order to avoid overprotective behaviour.

As regards parental attitude and education style, parent's expectations of TS could also be addressed in further research. Orten and Orten (1994) argue that the focus on

cognitive difficulties among girls with TS, due to the higher probability of learning disabilities found by the researchers, may lead parents to have low expectations of their child's abilities which, in turn, may affect their child's development.

To address the question of whether the emotional difficulties reported by researchers spring primarily from medical problems (height, infertility) or from monosomy, it would be very useful to compare women with TS with women affected by ovarian premature failure or with women with infertility problems and with normal subjects. It would also be useful to compare females with X-monosomy and females with mosaicism to other categories of patients with similar genetic conditions (Fragile X syndrome, Noonan syndrome). A more complex understanding of the origins of emotional difficulties is of utmost importance in order to develop good psychological methods and tools for reducing them.

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ATTACHMENTS

Questionnaire

Socio demographic information

Education and Job information

Achenbach's and Rescorla's Adult self report Questionnaire (2001)

World Health Organization Quality of life questionnaire-brief form (1998)

What is your sexual orientation ? ☐ Heterosexual ☐ Bisexual ☐ Homosexual

How many love relationships have you had? ...

Have you already had sexual intercourse? yes no

How much you would say you dislike the following components of your body? Mark the answer you feel right for you for each of the following components:

Chest never, seldom, sometimes, often, very often, always

Neck never, seldom, sometimes, often, very often, always

Breast never, seldom, sometimes, often, very often, always

Shoulders never, seldom, sometimes, often, very often, always

Stature never, seldom, sometimes, often, very often, always

Questions included only in the questionnaire version for women with TS:

How did you learn about your TS?

When (Age)....

Who informed you about TS? ...

In your opinion was the information you received complete?

In your experience was the way you were informed right?

What advice would you give about the way to inform people?

In your opinion is there something worrying about living with TS? If there is, could you describe your preoccupations?